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Prevalence of silent atrial fibrillation and cardiovascular disease in patients with obstructive sleep apnea

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ABSTRACT

Objective: Patients with silent and undiagnosed atrial fibrillation (AF) have increased risk of ischemic stroke. Patients with obstructive sleep apnea (OSA) have an increased risk of both AF and ischemic stroke. Our aim was to investigate the prevalence of silent AF and associated risk factors in patients investigated for OSA or with known OSA.

Methods: This prospective observational study was performed in two sites; one outpatient sleep-clinic at Zealand University Hospital and one private Ear-Nose- and Throat clinic. Patients were investigated with a type-3 portable sleep-monitoring device, while heart rhythm was home-monitored for 7 days with an event-triggered loop recorder. Patients were stratified in groups of mild, moderate and severe OSA based on Apnea-Hypopnea-Index (AHI).

Results: In a cohort of 303 patients, 238 (78.5%) were diagnosed with moderate/or severe OSA and 65 (21.5%) with no/mild OSA who constituted the control group. In 238 patients with moderate and severe OSA, AF was detected in 21 patients (8.8%) vs. 1 patient (1.5%,[$p=0.045$]) with mild OSA. Candidates for anticoagulation therapy were referred for further cardiovascular treatment. The majority of patients had known hypertension (n = 200,66%) and dyslipidemia (n = 235,[77.6%]) In patients with moderate/or severe OSA (AHI≥15), hypertension was more dysregulated ($p=0.005$) and more patients suffered from unknown prediabetes (n = 36, 3.1% vs. 14.3%[$p<0.001$]).

Conclusion: Undiagnosed AF and undertreated cardiovascular modifiable risk factors are common in a cohort of patients with OSA. With this study we propose that long-period home-monitoring in these patients is useful for identifying candidates for preventive anticoagulation, cardiovascular treatment and possibly prevent future ischemic stroke.

1. Introduction

In recent years, increasing attention have been directed towards sleep disordered breathing diseases (SDBs) such as obstructive sleep apnea (OSA). It is estimated, that approximately one billion people worldwide are affected by OSA and it has become one of the most common chronic diseases [1]. OSA is associated with both metabolic disturbances including obesity, insulin resistance, type 2 diabetes, and. metabolic syndrome. Cardiovascular diseases (CVD) such as hypertension, heart failure, coronary artery disease, stroke and atrial fibrillation (AF) are associated with OSA as independent risk factors [2].

AF is the most common sustained arrhythmia affecting 1–2% of people worldwide, and are frequently associated with OSA [3–7]. It has been shown in several epidemiologic studies that the risk of AF doubles in patients with sleep disordered breathing and quadruples with severe OSA [5,8]. Mechanisms leading to arrhythmia in patients with OSA include negative intrathoracic pressure, periodic hypoxemia and atrial remodeling [9]. Autonomic dysregulation of cardiac function leads to triggered activity seen as early and

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Abbreviations

AF	Atrial Fibrillation and flutter
AHI	Apnea hypopnea index
CABG	Coronary artery bypass grafting
CVD	Cardiovascular disease
CI	Confidence interval
EF	Ejection Fraction
ELR	External loop recorder
ENT	Ear, Nose and Throat
HFrEF	Heart failure with reduced ejection fraction
HR	Hazard Ratio
IHD	Ischemic heart disease
NNT	Number needed to treat
OR	Odds Ratio
OSA	Obstructive sleep apnea
OSAS	Obstructive sleep syndrome
SDB	Sleep disordered breathing
TIA	Transient ischemic attack

delayed after polarisations as well as abnormal automaticity caused by abnormal cardiac pulse formation, both precipitating arrhythmia [4,6,9]. OSA is an independent risk factor of cardioembolic ischemic stroke [10,11] and as comorbidities, AF and OSA are linked and both have shown to worsen neurological outcome in patients with acute ischaemic stroke [12].

The aim of this study was to determine the prevalence of undiagnosed and silent AF in patients with OSA using a 7-day external loop recorder (ELR) and to graduate AF prevalence and associated cardiovascular risk factors according to OSA-severity.

2. Methods

2.1. Study population

In this cross-sectional, prospective study, we investigated the prevalence of silent paroxysmal AF and cardiovascular risk factors in a population of patients investigated for OSA and in patients with known, moderate and severe OSA with an apnea-hypopnea-index (AHI) ≥15. We intended to enroll both patients with known OSA along with patients investigated for OSA resulting in a control-group with AHI <15 and a study group with AHI ≥15. In Denmark, the large majority of primary investigation of OSA in patients is performed in private Ear-, Nose-, and Throat (ENT)-clinics before they, in case of moderate or severe OSA with AHI ≥15, are referred to sleep-clinics in the secondary sector. Therefore, the secondary sector sleep clinics predominantly treat patients with moderate and severe OSA. The inclusion criteria for patients enrolled from the ENT clinics were suspected sleep disordered breathing with symptoms consistent with this (e.g. daytime sleepiness, irritability, reports of pauses in breathing during sleep from relatives). Inclusion criteria at sleep clinic was diagnosed OSA with AHI ≥1. For both were additional inclusion criteria age ≥18 and ability to informed consent. Patients were enrolled at their first visit at the ENT-clinic or at their first visit in the outpatient sleep clinic at the Department of Otorhinolaryngology and Maxillofacial Surgery, Zealand University Hospital in the period from Oct 1st-2018 -May 29th· 2020.

Exclusion criteria were patients with a history of known, documented ≥30 s of persistent or paroxysmal AF/flutter or patients in treatment with anticoagulation therapy for AF. This information was assessed by patient interview, review of medical records and ICD-10 codes from previous hospitalization. Additionally exclusion factors was incomplete ELR monitoring (signal time <5 days), incomplete or lack of blood samples or ECG and CPAP treatment already initiated.

Blood pressure, BMI, waist-hip-ratio and ECG was measured for all patients at the first visit at either the sleep clinic ambulatory or ENT private practice. For hypertension, diagnostic criteria were three consecutive blood pressure measurements at time of inclusion of at least 140 mmHg systolic or 90 mmHg diastolic pressure in a resting state or ongoing antihypertensive treatment. Hypertension was considered dysregulated if blood pressure measurements were above 140 mmHg systolic and/or 90 mmHg diastolic despite ongoing antihypertensive treatment.

Dyslipidaemia was defined by treatment with oral cholesterol lowering drugs or a total-cholesterol >5 mmol/L or triglycerides >2.6 mmol/L [13]. Metabolic syndrome was defined as central obesity (waist circumference >94 cm for men and >80 cm for women) and two of the following; triglycerides >1.7 mmol/L, or treatment; HDL >1.0 for men and >1.3 for women; resting fasting blood glucose >5.6 or previously diagnosed with type 2 diabetes; blood pressure >130/85 or treatment for hypertension [14,15]. IHD (ischemic heart disease) was classified as previous myocardial infarction, prevalent angina pectoris, percutaneous coronary intervention or coronary artery bypass surgery/grafting/stenting (CAGB). Family history of heart disease was defined as CVD in first-degree relative before age of 50 years men and 60 for women.

2.2. Outcome measures

2.2.1. Monitoring of heart rhythm

Detection of AF using home monitoring or a standard ECG was our primary outcome. AF was defined as at least 1 period of ≥30 s duration with irregular heart rhythm and without detectable p-waves and pattern more consistent with an alternative diagnosis [16].

A clinical event committee setting with cardiology specialists reviewed the recordings and adjudicated the primary outcome of AF/flutter. The device used (R.Test Evolution4®, NorDiaTech, France) is an external event-triggered ECG loop-recorder (ELR). The ELR analyses heart rhythm through continuous monitoring, and in case of an arrhythmic event, the device triggers automatically recording the specific episode. Patients were instructed to carry the device for 7 days, only to take off the device for short periods −e.g. during heavy-sweating exercise or while showering. Patients were asked about symptoms of arrhythmia (e.g. palpitations/angina) along with possible side-effects and whether they had removed the device prematurely.

2.2.2. Sleep examination

Sleep examination was performed for one night using a type-3 portable sleep-monitoring device. Type 3 monitors measure airflow, pulse, oxygen saturation, respiratory effort, and body position- and activity. In our study we used the NoxT3^{TM} device (ResMed, CA, USA). The device has previously been validated against polysomnography (PSG) [17]. Sleep analysis was performed blinded to the heart rhythm monitoring results. Disorders within the field of impaired sleep includes OSA, central sleep apnea, sleep-related hypoxemia disorder and sleep-related hypoventilation syndrome [18]. When characterizing OSA, respiratory disturbances are expressed as numbers of apneas and hypopneas per hours sleep [18].

An apnea was defined as pause of airflow for the duration of at least 10 s. An obstructive sleep apnea was defined as events with respiratory effort throughout the episode of an apnea. A central apnea was defined as apnea with no respiratory effort throughout

the event. Hypopneas were defined as a ≥30% drop in airflow for the duration of at least 10 s with a ≥3% desaturation of oxygen. Mixed apneas were categorized as apneas with partial absent respiratory effort and partial presence of respiratory effort through the episode-period. The severity of OSA was defined by AHI including the number of both obstructive, mixed and hypopneas per hour of sleep [18,19] The AHI is the mean number of apneas per hour of sleep. AHI below 5 was considered normal, 5 to <15 was defined as mild OSA, AHI of 15 to <30 were moderate OSA and an AHI ≥30 was defined as severe OSA. The oxygen desaturation-index was defined as the average number of desaturations ≥4% per hour of sleep. Subjective daytime sleepiness was assessed for each patient with Epworth sleepiness scale (ESS). Sleep time was calculated from total recording time, and only sleep-examinations of ≥4 h of sleep with a quality of at least 90% was accepted [18,20].

2.3. Statistics

Based on prior studies of patients with OSA and AF, we performed an a priori power calculation and estimated that a sample size of 300 patients with OSA would provide 80% power and a 0.05 alpha to detect AF in approximately 6.5%. Categorical baseline data are presented in absolute numbers (percentages) and continuous variables as means (± standard deviation (SD)). Categorical data were compared with the χ^2 test and continuous variables with an unpaired *t*-test. Multiple logistic regression with backward elimination are listed as odds ratios (OR) with confidence intervals (95% CI) and were used to identify factors independently associated with AF and AHI. All tests were two-sided, and a value of <0.05 was considered statistically significant. Analyses were performed using Rstudio v.1.1.463 and SPSS v.28 for MAC/OSX.

2.4. Ethics

The study was conducted in accordance with the Helsinki Declaration. Informed consent was obtained from all patients and the protocol was reviewed by the Danish Regional Ethics Committee and The Danish Data Protection Agency and both granted study permission *(protocol-number: SJ-714)* and *(case-number: reg-033-2018).*

3. Results

3.1. Baseline data

Of 498 patients screened for study inclusion, a total of 303 were included from both sites with 183 (60.4%) from the ENT hospital department and 120 (39.6%) from the private ENT clinic for the final study population. In total, 192 out of 495 patients were excluded due to incomplete heart monitoring with <5 days recording time, known AF or anticoagulation treatment, incomplete blood samples or no ECG performed or lack of interest in study (Fig. 1). Of patients excluded due to incomplete monitoring/premature removal of the device, none presented with AF during the days of monitoring.

In total, 238 patients had AHI ≥15 and 65 patients had AHI <15 (Fig. 1).

Table 1 shows baseline characteristics of patients classified by severity of OSA. Hypertension, type 2 diabetes, prediabetes, BMI, waist/hip ratio, blood pressure and heart rate were all significantly and positively associated with increasing severity of OSA (Table 1).

A study total of 66% had hypertension and the prevalence was higher in the groups with moderate (64.5%) to severe (77.2%) OSA [$p < 0.001$]. Among all patients with hypertension, 27.7% were dysregulated and 25.7% of patients were unaware of their hypertension. Patients with moderate and severe OSA had more dysregulated hypertension (25.8% and 36.2%, *[p=0.005]*) compared to patients with AHI <15. Patients with moderate and severe OSA were numerically more frequently unaware of their hypertension (26.9% and 28.3% respectively) compared to patients with mild OSA (18.5%), however the difference did not reach statistical significance *[p=0.31, ns]*). One patient was admitted acutely to the emergency department for treatment due to an office blood pressure of >215/105 mm Hg. Dyslipidaemia was predominate as 77.6% of all patients were affected and a trend of higher prevalence was found in groups of moderate and severe OSA (78.5% and 81.4% respectively) vs. 67.7% with mild OSA *[p=0.086])*. Metabolic syndrome was present in 70.0% of the total cohort, and in 75.3% of patients with moderate OSA and 78.6% of patients with severe OSA ($p < 0.001$)(Table 1). Type 2 diabetes was present in 15.8% in the cohort of which 18.8% was unknown (n = 9).

3.2. Sleep examination

Mean AHI of all 303 patients was 34.2, with a range from 0.2 to 115.8. Patients with moderate and severe sleep apnea had more central sleep apneas compared to the control group. Mean amount of episodes of central apneas in the total cohort was 10.2 apneas per hour, and only one patient presented with primary central sleep apnea syndrome (CSA). Patients with severe OSA (AHI ≥30) had a mean of 36.4 central apneas per hour. This was significantly more central events compared to patients with moderate OSA ($p < 0.001$)(Table 1).

3.3. Home monitoring with external ECG loop recorder (ELR)

We detected AF in 22 patients with the 7 day-recording with ELR with an AF prevalence in the total cohort of 303 patients (AHI range 0.1–115) of 7.3%. All patients presented with asymptomatic and paroxysmal AF. Fig. 2 illustrates a standard tracing of paroxysmal AF in one patient with OSA.

There was a significant difference in the AF prevalence of 8.8% (21 out of 238 patients) in patients with moderate and severe OSA (AHI >15) versus 1.5% (1 out of 65 patients) in the group of mild OSA (*p=0.045)*. AF was diagnosed most frequently in patients with severe OSA (AHI >30) (10.7%, 14 out of 131 patients) (Fig. 3).

Mean AF-burden in all AF patients was 16.5 h (range 0.008–149.5 h). The only patient presenting with AF and AHI <15 (AHI 0.2) was 54 years and had previously had acute ischaemic stroke and a formerly performed rhythm monitoring for two days had not shown AF. Additional information of AF burden and duration of episodes are illustrated in Table 2. Supraventricular extra systoles (SVES) were found in more than 1 in 5 patients in the whole cohort, non-sustained ventricular tachycardia was identified in 24 patients (7.9%) and substantial nocturnal pauses were registered in 5 patients (1.7%) with a duration range of 2.2–9.6 s.

In multiple regression analysis, AHI, CHADSVASc and package-years remained significantly and positively associated with AF, while a higher BMI was negatively associated with AF.

All candidates for anticoagulation therapy were referred to the local department of cardiology for further clinical examination and initiation of anticoagulation therapy. Echocardiogram was performed in all 22 referred patients. None of the 22 patients with AF had heart failure with reduced ejection fraction (HFrEF) with EF <40%. The majority of the 22 patients (68.2%, n = 15) had normal EF and ventricle function. Seven patients (32%) had mild hypertrophic left ventricles of which three had EF in the range of 40–50%. No patients had significant valvular disease (Table 3).

4. Discussion

In this observational cross-sectional study, we found a high

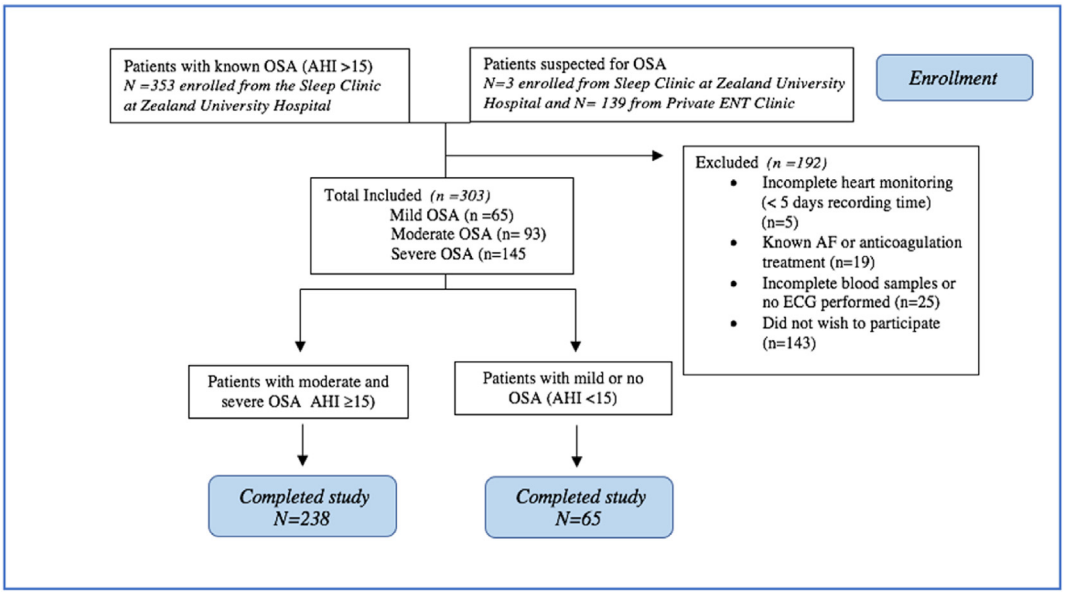

Fig. 1. Enrollment. AF: atrial fibrillation. AHI: apnea-hypopnea index. ECG: electrocardiogram. ENT: ear, nose and throat. OSA: obstructive sleep apnea.

prevalence of silent and paroxysmal AF in patients with OSA examined with 7-day home monitoring by an external ECG loop recorder. The AF prevalence significantly increased - along with modifiable cardiovascular risk factors - with OSA-severity. The AF prevalence seen in our control group is comparable to a previously reported prevalence in a background population with similar age demographics [3]. Our finding of a higher prevalence of AF among patients with OSA is also consistent with previous studies [5,7,21–24]. Many studies have investigated the epidemiology of OSA in patients with AF, but much less have studied the opposite relation. The prevalence of AF amongst patients with OSA has previously been investigated using different ECG-techniques. However, to our knowledge, no previous study has examined patients with OSA and no previous diagnosis of AF, including both moderate and severe OSA (AF ≥15) with extended/long-time hearth monitoring. One study from 2004 reported severe bradyarrhythmia in 23 patients with OSA, diagnosed with implanted loop-recorders of 16 months, but did not report on AF occurrence [25]. Another study investigated 25 patients with severe OSA (AHI ≥30) with implanted loop-recorders for three years and found AF (≥10 s) in five patients (20%) [26]. In 2014 Chanda et al. [27] investigated 20 patients with severe OSA (AHI ≥30) with 7 days of monitoring with an outpatient event ECG-recorder (Model ER920W, eCardio, Houston, TX), finding AF of 7 s duration in 1 patient.

Some studies have examined the association between OSA and AF in larger populations. In a subpopulation of The Sleep Health Heart study [5], investigators found a AF prevalence of 4.8% in 228 patients, however this study only included patients with a respiratory disturbance index (RDI, events including apneas and hypopneas) ≥30 with ECG-data obtained from one-night PSG monitoring.

Our study is most comparable with a Swedish study by Hendrikx el al. [21], that investigated the association of OSA and AF over time with home-monitoring of heart rhythm with a hand-held ECG recorder for 30 s twice a day and/or at occurrence of symptoms. They found an AF prevalence of 6.5% and included patients with known AF. A large Danish registry study from 2014 of 4.5 million persons investigated the relationship of OSA, treatment with or without CPAP and the risk of myocardial infarction (MI) and ischemic stroke and found a 4% prevalence of AF in patients with OSA and 4.9% prevalence in patients with sleep apnea receiving CPAP [23]. Another large retrospective cohort study of 3.542 OSA patients found a similar AF incidence of 4.3% [24]. The registry-based design of these large studies most likely explains the lower AF prevalence in comparison to our findings.

In our study we only included patients without previously diagnosed AF, nevertheless we found a higher prevalence of silent AF than all the above-mentioned studies. To our knowledge, AF has not been investigated in patients with OSA using ELR, and we consider the higher prevalence of AF in our cohort as a possible result of a longer time of hearth-rhythm monitoring in a population where AF seems to appear paroxysmally.

In univariate analysis, we found a dose-response relationship with the severity of OSA and several cardiovascular comorbidities including hypertension, dyslipidaemia, type 2 diabetes, prediabetes, metabolic syndrome and central sleep apnea. Prevalence of type 2 diabetes among patients with OSA has previously been described [28] at a range of 15–30% with an increasing prevalence with increasing severity of OSA. Our results, with a prevalence of 14 and 21% support these studies.

We found that one in four patients had unknown hypertension regardless of AHI and more than three in four had dyslipidaemia, of which approximately 50% was unknown. An association between nocturnal OSA and daytime hypertension has previously been shown [29], even after adjusting for BMI, as obesity is considered a substantial confounder. A large prospective study has demonstrated the dose-response of severity of OSA and cumulative incidence of hypertension [29]. This is consistent with our findings of a high prevalence of hypertension in patents with OSA.

In multiple logistic regression analysis, AHI, CHADSVASc and package-years remained significantly and positively associated with AF. However, in this adjusted model, higher BMI was somewhat surprisingly, negatively associated with AF. This could imply that given a patient is healthy and does not suffer from OSA, CHADSVASC risk-factors or if the patients has a current or former smoking habit, overweight per se may not convey additional risk to developing AF. In fact, being lean (and tall) could indicate a higher risk of developing AF [30] than an elevated BMI without all the associated risk factors (Table 4).

Table 1
Characteristics of patients with mild, moderate and severe OSA, examined for comorbidities, mean (SD).

	All Patients (n = 303)	Patients with AHI <15 (n = 65)	Patients with AHI 15–30 *(n=93)*	Patients with AHI >30 *(n = 145)*	*p-value*
Male, n (%)	208 (68.6)	*37 (56.9)*	61 (65.6)	110 (75.9)	***0.018***
Age, years, mean (SD)	56.4 (12.4)	50.2 (13.1)	57.6 (11.5)	57.6 (11.9)	***<0.001***
Hypertension, n %	200 (66.0)	28 (43.1)	60 (64.5)	112 (77.2)	***<0.001***
Hypertension, dysregulated, n%	84 (27.7)	9 (13.8)	24 (25.8)	51 (35.2)	***0.005***
Hypertension, unknown, n %	78 (25.7)	12 (18.5)	25 (26.9)	41(28.3)	*0.31*
Dyslipidaemia, n %	235 (77.6)	44 (67.7)	73 (78.5)	118 (81.4)	*0.086*
Dyslipidaemia, unknown n, %	151 (49.8)	31(47.7)	48 (51.6)	72 (49.7)	*0.89*
BMI, kg/m2, mean (SD)	31.6 (6.6)	29.6 (5.6)	31.0 (6.6)	32.9 (6.8)	***0.002***
Type 2 diabetes, n %	48 (15.8)	4 (6.2)	13 (14.0)	31 (21.4)	*0.017*
Type 2 diabetes unknown, n	9 (2.9)	1 (1.5)	2 (2.2)	6 (4.1)	*0.505*
Prediabetes, n % (HbA1c 42–47 mmol/L)	36 (11.8)	2 (3.1)	13 (14.0))	21 (14.5)	***0.046***
Diabetes duration, years, (SD)	4.7 (7.8)	2.2 (2.0)	7.7 (12.6)	3.7 (4.9)	*0.26*
History of prior ischemic stroke, n %	11 (3.6)	1 (1.5)	2 (2.2)	6 (4.1)	*0.51*
History of prior UAP, n %	3 (1.0)	1 (1.5)	1 (1.1)	1 (0.7)	*0.84*
History of prior stable AP, n %	12 (3.9)	1 (1.5)	2 (2.2)	9 (6.2)	*0.16*
Prior AMI, n %	10 (3.3)	1 (1.5)	4 (4.3)	5 (3.5)	*0.93*
IHD, n %	11 (3.6)	1 (1.5)	3 (3.2)	7 (4.8)	*0.48*
History of CABG, n %	4 (1.3)	0	2 (2.2)	2 (1.4)	*0.51*
Family history of IHD, n (%)	74 (24.4)	12 (18.5)	19 (20.4)	43 (30.0)	*0.12*
Pack-years, cigarettes, mean, (SD)	13.9 (17.5)	7.6 (9.7)	15.3 (18.1)	15.9 (19.2)	***0.004***
Active smokers, n, %	81 (26.7)	13 (20)	25 (26.9)	43 (29.7)	*0.34*
Thyroid disease, n %	10 (3.3)	1 (1.5)	3 (3.2)	6 (4.1)	*0.62*
HbA1c mmol/mol, mean, (SD)	40.0 (10.2)	36.8 (11.4)	38.7 (7.5)	42.3 (10.6)	***<0.001***
Triglyceride, mmol/L, mean (SD)	2.2 (1.5)	1.8 (1.4)	2.1 (1.2)	2.4 (1.7)	***0.019***
Total cholesterol mmol/L, mean (SD)	5.2 (1.1)	5.9 (5.9)	5.2 (1.1)	5.1 (1.0)	*0.14*
LDL cholesterol mmol/L, mean (SD)[a]	2.9 (0.9)	3.1 (1.0)	2.9 (0.9)	2.8 (1.0	*0.07*
LDL cholesterol mmol/L, mean (SD)[b]	2.9 (0.9)	3.1 (1.1)	2.9 (0.9)	2.8 (1.0)	*0.13*
Waist/hip ratio, mean, (SD)	1.0 (0.1)	0.9 (1.2)	1.0 (0.1)	1.0 (0.1)	***<0.001***
Systolic blood pressure, mmHg, mean (SD)	143.7 (19.9)	134.9 (17.6)	144.5 (18.3)	147.3(20.9)	***<0.001***
Diastolic blood pressure, mmHg, mean (SD)	88.2 (11.8)	87.3 (10.3)	85.6 (10.4)	90.3 (12.9)	***0.009***
Heart-rate, mean (SD)	72.4 (12.8)	70.8 (14.2)	68.8 (11.3)	75.6 (12.5)	***<0.001***
Metabolic syndrome	212 (70.0)	28 (43.0)	70 (75.3)	114 (78.6)	***<0.001***
Central apneas, mean (SD)	10.3 (26.3)	2.1 (3.3)	6.0 (8.1)	16.8 (36.4)	***<0.001***
Epworth Score	9.9 (4.8)	9.5 (4.1)	9.9 (4.9)	10.1 (5.1)	*0.73*

Data shown as mean value, SD unless indicated otherwise. For continuous data comparisons, unpaired *t*-test was used, while chi-square test was used for nominal data. Baseline characteristics before initiating CPAP treatment.
AHI: apnea-hypopnea-index, Dysregulated hypertension: patients treated pharmacological for hypertension with blood pressure at consult >140 systolic and/or 90 diastolic mmHg measured 3 times at resting state. Dyslipidemia: Treatment with oral cholesterol-lowering drugs or total cholesterol >5 mmol/L or triglycerides >2.6 mmol/L. Metabolic syndrome: central obesity (waist circumference >94 cm for men and >80 cm for women) and two of the following; triglycerides >1.7 mmol/L, or treatment; HDL >1.0 for men and >1.3 for women; resting fasting blood glucose >5.6 or previously diagnosed with type 2 diabetes; blood pressure >130/85 or treatment for hypertension. OSA: obstructive sleep apnea. SD: standard deviation (International Diabetes Federation guidelines [37].
[a] Missing blood samples from 20 patients due to very high triglycerides, the formula of Friedewald is not used on these patients.
[b] Calculated LDL in all 303 patients using Friedewald's formula.

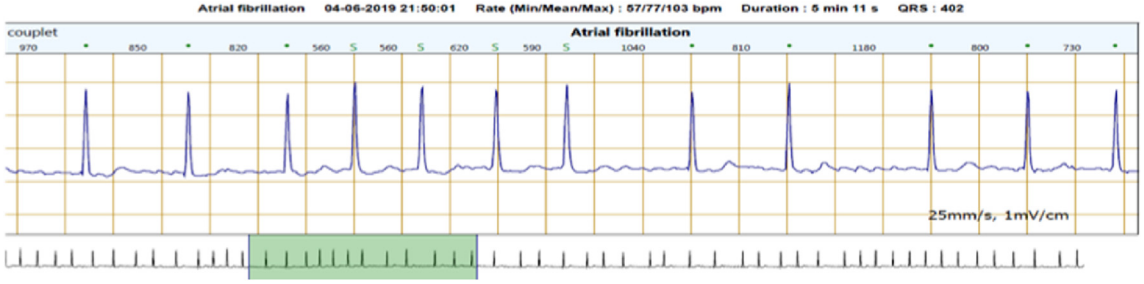

Fig. 2. Standard electrocardiography tracing of atrial fibrillation in a patient with obstructive sleep apnea.

Although AF has repeatedly been linked to a higher cardio-embolic risk, it is important to acknowledge that structural and functional remodeling in the atria, such as atrial myopathy with increased atrial volumes, fibrosis and reduced atrial function, can cause thrombo-embolic episodes, regardless of the presence of AF. Atrial myopathy is among other conditions influenced by obesity, hypertension diabetes and OSA. These conditions independently affect and lead to atrial dysfunction, why not all cardioembolic events can be attributed to paroxysmal AF [31,32].

The amount of central apneas increased significantly with OSA severity, however in our study, we were not able to significantly associate central sleep apneas to AF in multivariate analysis. This might be explained by our relatively small control group size. In contrast, the Sleep Health Heart study has linked central sleep apnea to incident AF, even after adjusting for cardiovascular risk factors [33] with a 2–3 fold increase of odds for development of AF.

Investigation of OSA and screening for potential comorbidities in each patient, initiation of treatment and control differ among

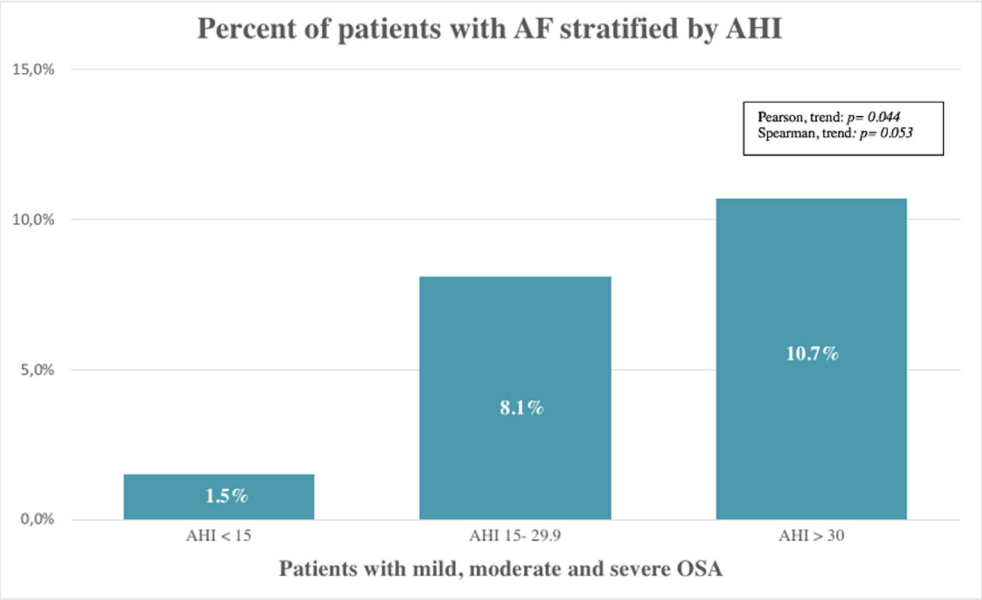

Fig. 3. Percentage of patients with AF >30 s (n = 22) among all patients (n = 303) stratified by AHI. AHI <15 (n = 1 of 65 patients). AHI 15–29.9 (n = 7 of 93 patients), AHI ≥30 (n = 14 of 145 patients). P-values are given for trend. AF: atrial fibrillation. AHI: apnea-hypopnea index. OSA: obstructive sleep apnea.

Table 2
Characteristics of patients diagnosed with atrial fibrillation.

Time to first episode of AF, hours	Total AF burden, hh:min:sec	Number of episodes	Monitoring time dd:hh:min	Other findings
1	00:37:00	19	06:16:56	EAT, PSVT
47	00:02:00	1	06:20:52	PVC in bigeminy, trigeminy, non-sustained VT
0	30:18:00	1053	06:01:01	–
36	00:06:00	4	06:06:11	–
1	84:54:00	904	07:01:44	–
135	00:02:00	1	06:19:40	PVC in bigeminy
153	00:04:00	4	08:07:53	–
0	140:21:00	91	06:15.16	non-sustained VT
39	03:59:00	75	06:23:20	–
36	27:26:00	240	06:14:24	–
120	00:02:00	2	06:14:40	Non-sustained VT
19	00:23:00	7	06:20:16	PSVT, non-sustained VT
141	00:00:30	1	06:15:00	PSVT, non-sustained VT
23	05:38:00	167	06:20:56	–
134	00:08:00	1	06:00:14	–
28	00:36:00	21	05:18:00	–
46	06:35:00	120	07:02:41	PSVT
66[a]	00:11:00	2	06:23:20	–
39	00:31:00	10	06:20:16	–
34	13:03:00	291	07:04:04	EAT
5	00:05:00	3	07:04:32	–
98	05:45:00	40	07:11:13	–

[a] episode of atrial flutter. AF: atrial fibrillation, EAT: ectopical atrial tachycardia, PSVT: paroxysmal supraventricular tachycardia, PVC: premature ventricular contractions, VT: ventricular tachycardia.

regions in Denmark. To our knowledge there are no national or international guidelines regarding systematic opportunistic screening for comorbidities in patients with OSA, why management of OSA patients diverges. The 2020 European Society of Cardiology (ESC) guideline for the diagnosis and management of AF recommends opportunistic screening for OSA in patients with known AF (type IIa recommendation) [16]. The American Academy of Sleep Medicine (AASM) recommends "*general education of the impact of weight loss, sleep position, alcohol consumption, risk factor modification, and medication effects*". AASM state that patient education should optimally "*be delivered as part of a multidisciplinary chronic disease management team*"[34]. In this context, the high prevalence of AF amongst patients with OSA might warrant a recommendation of screening for paroxysmal AF and could be valuable in the management of modifiable cardiovascular risk factors in patients with OSA.

5. Limitations

We did not use PSG for evaluation OSA. However, NoxT3^{TM} device is a pragmatic and well-accepted method for OSA-examination and most frequently used as diagnostic method. Moreover we did not use Holter monitoring. The device used in this present study has previously performed well in comparison to Holter in a study of patients with TIA or ischemic stroke [35] and a recent meta-analysis stated that portable devices have possible benefits over

Table 3
Echocardiography findings in patients with atrial fibrillation.

Patient no:	LV	LVEF	Valvular disease	Atrium sizes	Other findings
1	Mild hypertrophic LV	Normal	Mild aortic insufficiency	Normal	–
2	Normal	Normal	–	Normal	–
3	Normal	50%		LA moderately dilated	Mildly dilated RV
4	Normal	Normal		Normal	Mildly dilated RV
5	Mild hypertrophic LV	40%	–	Moderate dilated atriums	–
6	Normal	Normal	Mild mitral insuffiency + mild tricuspid insufficiency	LA mildly dilated	–
7	Mild hypertrophic LV	Normal	Mild tricuspid insuffiency	Normal	Mildly dilated aorta asc
8	Normal	40%	Mild mitral insuffiency	RA + LA dilated	–
9	Mild hypertrophic LV	Normal	–	Normal	Moderate aortic ectasia
10	Normal	Normal	Mild mitral insuffiency	Normal	–
11	Mild hypertrophic LV	45 −50%	–	Normal	–
12	Normal	Normal	–	Normal	–
13	Mild hypertrophic LV	Normal	Mild mitral insufficiency + sclerotic mitral valve + mild mitral insuffiency	LA severely dilated	–
14	Normal	Normal	–	Normal	–
15	Normal	Normal	–	Normal	–
16	Normal	Normal	–	Normal	–
17	Normal	Normal	–	Normal	–
18	Normal	Normal	–	Normal	–
19	Normal	Normal	Mild aortic stenosis	Normal	–
20	Normal	>55%	Sclerotic and mildly insufficient tricuspid valve + mild aortic insufficiency + mild mitral insufficiency	Normal	–
21	Mild hypertrophic LV	45%	–	Normal	–
22	Normal	Normal	–	Normal	–

LA: left atrium.LV: left ventricle. LVEF: left ventricle ejection fraction. RA: right atrium. RV: right ventricle.

Table 4
Adjusted odds ratio in multiple logistic regression analysis for AF.

	Odds Ratio	95% CI for exp. Odds Ratio		*p-value*
		Lower	Upper	
AHI	1.01	1.0	1.0	0.027
BMI	0.91	0.8	1.0	0.040
Package-years	1.02	1.0	1.0	0.028
CHA_2DS_2VASc	1.61	1.6	2.3	0.005

Multiple regression analysis, backward stepwise elimination for AHI and covariates and atrial fibrillation as the dependent variable.
Variables in the model were known risk factors for atrial fibrillation in addition to baseline variables with a p-value < 0.1 from Table 1 were entered in the multiple logistic regression model: age, gender, hypertension, dyslipidaemia, dysregulated hypertension, diabetes, pre-diabetes, BMI, triglyceride status, CHA_2DS_2VASc, current smoking status, metabolic syndrome and AHI.
AF: atrial fibrillation. AHI: apnea-hypopnea-index. BMI: body-mass-index. CI: confidence-interval.

Holter, especially in the matter of large population screening, as the analysis is much less time consuming [36].

Taking into consideration that healthcare systems as well as procedures for referral of patients with OSA differ among countries and even inside regions, it might not be possible to one-to-one extrapolate the results of this study to all healthcare practices.

6. Conclusion

We believe our study supports the alignment of the systematic screening and management of potential comorbidities associated with OSA, especially silent AF, prediabetes and diabetes, hypertension and hyperlipidaemia, to the benefit of OSA patients in the future. This study has to our knowledge, the highest prevalence of silent, paroxysmal AF in an observational study including both patients with moderate and severe OSA. Silent and paroxysmal AF with the following indication for anticoagulation treatment, along with modifiable cardiovascular risk factors such as hypertension, dyslipidaemia, prediabetes and type-2 diabetes, are common among patients with moderate and severe OSA. Screening tools for AF must be patient-friendly, reliable and little time-consuming, why ELR devices seems applicable for practice in a broader perspective. Opportunistic screening and home-monitoring in patients with moderate to severe OSA for paroxysmal AF and modifiable cardiovascular risk factors should be considered as tool in the prevention of potentially future strokes.

Author statement

This study was designed, directed and coordinated by AH, TB, MMS, PT and PH. As the principal investigator AH planned, performed and carried out the study. AH and MMS participated in clinical committees and PH additionally contributed in analysing data. AH performed the statistical analysis with MMS and PH who also helped to draft the manuscript.

All authors have read, commented and approved the final manuscript.

Declaration of competing interest

Author AH, MMS, PT, TB and PH declared no conflict of interest.

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